Tuder, Rubin M.
Departments of Pathology and Medicine, Division of Pulmonary Sciences and Critical Care Medicine, Pulmonary Hypertension Center, Denver, CO, 80262, USA

ORPORATE SOURCE:

OURCE: Am. J. Respir. Cell Mol. Biol. (1997), 17(6), 748-756
CODEN: AJRBEL; ISSN: 1044-1549

UBLISHER: American Lung Association

OCUMENT TYPE: Journal

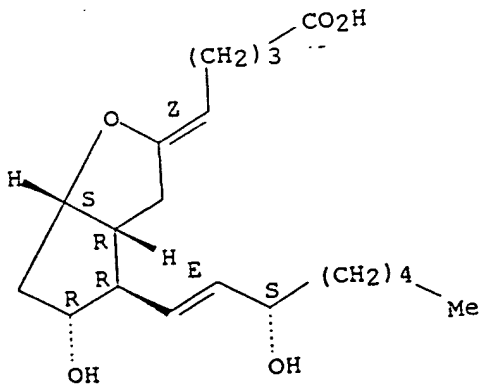
ANGUAGE: English

AB Prostaglandins have emerged as a therapeutic option for patients with **peripheral vascular disease** as well as pulmonary hypertension as a means to increase blood flow. The authors tested the hypothesis that prostaglandins regulate vascular endothelial growth factor (VEGF) expression in the human monocytic THP-1 cell line and in isolated perfused rat lungs. The data show that the stable PGI2-analog iloprost induces VEGF gene expression (predominantly VEGF121, but also VEGF165 isoforms) and VEGF protein synthesis in THP-1 cells. This effect is abolished by dexamethasone and by Rp-cAMP, a specific inhibitor of cAMP-dependent protein kinase (PKA) activation. The calcium channel blocker diltiazem has no effect on the iloprost-induced VEGF gene expression, and depletion of intracellular Ca2+ stores by long-term exposure (16 h) of THP-1 cells to thapsigargin does not inhibit iloprost-induced VEGF gene expression, suggesting that an increase in intracellular Ca2+ is not essential for VEGF gene induction by iloprost. However, an increase of intracellular Ca2+ by a short-term (2 h) exposure of THP-1 cells to thapsigargin or to the calcium-ionophore A23187 increases VEGF mRNA levels, indicating that a change in intracellular Ca2+ by itself can alter VEGF gene expression. The effects of thapsigargin or A23187 on VEGF gene expression are also mediated via cAMP-PKA since they are inhibited by Rp-cAMP. In isolated perfused rat lungs, PGI2 and PGE2 increases VEGF mRNA abundance, whereas Rp-cAMP inhibits the prostaglandin-induced VEGF gene activation. Thus, the authors' data suggest that prostaglandins stimulate VEGF gene expression in monocytic cells and in rat lungs via a cAMP-dependent mechanism.

IT **35121-78-9**, PGI2
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(prostaglandins induce VEGF expression in human monocytic cell line and rat lungs via cAMP)

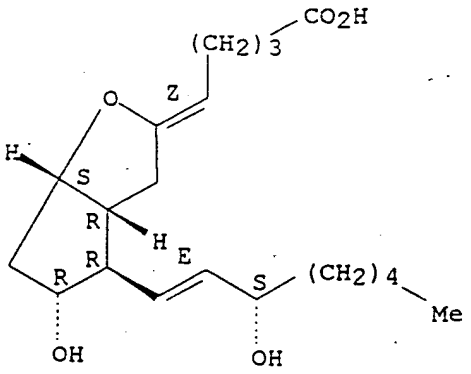
RN 35121-78-9 CAPLUS
CN Prosta-5,13-dien-1-oic acid, 6,9-epoxy-11,15-dihydroxy-, (5Z,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



PUBLISHER: Tongji Medical University
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to investigate the effect of low high-d.-lipoprotein (HDL) combined with hypertriglyceridemia in coronary artery disease (CAD) patients on prostaglandin I2 (PGI2) biol. activity in relation to lipid regulating treatment with fenofibrate. The inhibitory rate of PGI2 on ADP-induced platelet aggregation was used as the index for PGI2 biol. activity. Twenty health individuals served as normal controls. CAD group consisted of 20 patients with low HDL combined with hypertriglyceridemia. The results showed that, before the treatment, the stabilizing effect on PGI2 activity decreased significantly in CAD group when compared with the control group ($P < 0.01$). One month after the treatment, HDL level in CAD group increased significantly and TG level significantly decreased ($P < 0.001$). The different effect on PGI2 activity was no longer found between CAD group and control group ($P > 0.05$), further confirming the protecting risk factor of CAD, therefore, impaired PGI2 biol. activity and increased platelet aggregation might be responsible mechanisms. Furthermore, raising HDL level by lipid regulating treatment could restore the protective effect of HDL on PGI2 and might be helpful in the prevention of the acute coronary syndrome.
IT 35121-78-9, PGI2
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(effect of low HDL combined with hypertriglyceridemia in coronary artery disease patients on PGI2 biol. activity in relation to lipid regulating treatment)
RN 35121-78-9 CAPLUS
CN Prosta-5,13-dien-1-oic acid, 6,9-epoxy-11,15-dihydroxy-, (5Z,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



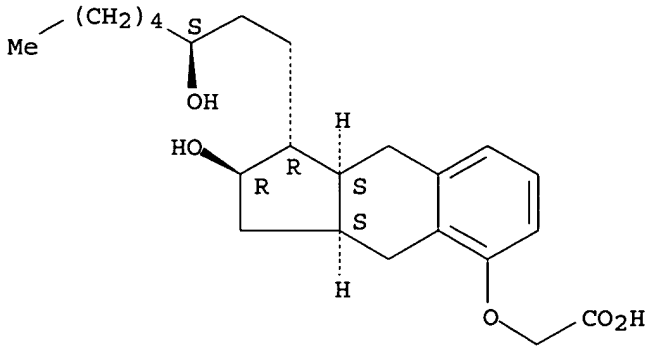
REFERENCE COUNT: 1
REFERENCE(S): (1) Aoyama, T; Prostaglandin I2 half life regulated by high density lipoprotein is decreased in acture myocardial infarction and unstable angina pectoris

L87 ANSWER 32 OF 53 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:805105 CAPLUS
DOCUMENT NUMBER: 128:98033
TITLE: Prostaglandins induce vascular endothelial growth factor in a human monocytic cell line and rat lungs via cAMP
AUTHOR(S): Hoper, Marius M.; Voelkel, Norbert F.; Bates, Thomas O.; Allard, Jenny D.; Horan, Marilee; Shepherd, David; Searched by Barb O'Bryen, STIC 308-4291

L15 ANSWER 12 OF 29 CAPLUS COPYRIGHT 2001 ACS
TI Therapeutic efficacy of allergen-monomethoxy **polyethylene glycol** conjugates in the treatment of allergen-induced asthmatic responses in guinea pigs
AN 1997:282918 CAPLUS
DN 126:347227
TI Therapeutic efficacy of allergen-monomethoxy **polyethylene glycol** conjugates in the treatment of allergen-induced asthmatic responses in guinea pigs
AU I-Ijima, Hiroaki; Bitoh, Soji; Hashimoto, Ken-Ichi; Kurishima, Koichi; Nomura, Akihiko; Sakamoto, Toru; Goto, Yukio; Lang, Glen M.; Sehon, Alec H.; et al.
CS Department of Pulmonary Medicine, Institute of Clinical Medicine, University of Tsukuba, Japan
SO Int. Arch. Allergy Immunol. (1997), 113(1-3), 323-325
CODEN: IAAIEG; ISSN: 1018-2438
PB Karger
DT Journal
LA English
AB Allergen-sensitized guinea pigs were used as animal models for asthma and for the study of therapeutic efficacy of an allergen-monomethoxy **polyethylene glycol** conjugate. **Administration** of the conjugate by **inhalation** led to partial suppression of the immediate asthmatic response and to obliteration of the late asthmatic response.

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 289480-64-4 REGISTRY
CN Acetic acid, [[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, monosodium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Remodulin**
CN Treprostinil sodium
FS STEREOSEARCH
MF C23 H34 O5 . Na
SR CAS Registry Services
LC STN Files: BIOSIS, CA, CAPLUS, IPA, SYNTHLINE, TOXCENTER
CRN (81846-19-7)

Absolute stereochemistry.



● Na

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> file medicine
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	6.70	6.91

FILE 'ADISCTI' ENTERED AT 13:26:20 ON 17 MAR 2003
COPYRIGHT (C) 2003 Adis International Ltd. (ADIS)

FILE 'ADISINSIGHT' ENTERED AT 13:26:20 ON 17 MAR 2003
COPYRIGHT (C) 2003 Adis International Ltd. (ADIS)

FILE 'ADISNEWS' ENTERED AT 13:26:20 ON 17 MAR 2003
COPYRIGHT (C) 2003 Adis International Ltd. (ADIS)

FILE 'BIOSIS' ENTERED AT 13:26:20 ON 17 MAR 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'BIOTECHNO' ENTERED AT 13:26:20 ON 17 MAR 2003
COPYRIGHT (C) 2003 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'CANCERLIT' ENTERED AT 13:26:20 ON 17 MAR 2003

FILE 'CAPLUS' ENTERED AT 13:26:20 ON 17 MAR 2003

FILE 'CEN' ENTERED AT 13:26:20 ON 17 MAR 2003

FILE 'DDFB' ACCESS NOT AUTHORIZED

L2 ANSWER 1 OF 20 ADISINSIGHT COPYRIGHT 2003 (ADIS)
CN Treprostinil
CN **15AU; 15AU81; BW 15AU; BW 15AU81; BW A15AU; LRX 15; Remodulin; treprostinol; U 62840; Uniprost; UT 15**
CN (1R,2R,3aS,9aS)-((2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-((3S)-3-hydroxyoctyl)-1H-benz(f)inden-5-yl)oxy)acetic acid
DSTA . . . World, Pulmonary hypertension
Phase II, United States, Peripheral arterial occlusive disorders
Phase II, World, Peripheral vascular disorders
Phase I, World, **Cancer**
Discontinued II, United Kingdom, Congestive heart failure
. . . Treprostinil (treprostinil sodium, UT 15, U 62840, LRX 15, 15AU81, BW A15AU, BW 15AU, 15AU, BW 15AU81, treprostinol, Uniprost sup(TM), **Remodulin** sup(TM)) is a stable, long acting prostacyclin analogue developed to be administered subcutaneously. Treprostinil is administered using a `pager-sized MiniMed. . . FDA by 2 June 2004. Priority Healthcare was selected by United Therapeutics to manage the phase IV study.

Treprostinil, as **Remodulin** sup(TM), is available through Priority Healthcare and Accredo Therapeutics (formerly Gentiva Health Services), United Therapeutics' US distributors.

In February 2002, the Canadian Therapeutics Products Directorate (TPD) accepted **Remodulin** sup(TM) for review as a New Drug Submission (NDS) for the treatment of pulmonary arterial hypertension. The TPD have also granted **Remodulin** sup(TM) a priority review status. The application was approved in October 2002.

In November 2002, United Therapeutics announced that. . . with additional European filings after treprostinil has been approved in France. United Therapeutics have also submitted a marketing application for **Remodulin** sup(TM) in Switzerland and Australia.

Initially the name Uniprost sup(TM) was to be used but the name **Remodulin** sup(TM) is to be the tradename for treprostinil in the USA and Europe.

In January 2003, results from 3. . . the UK. However, development has been discontinued in this indication. Glaxo Wellcome merged with SmithKline Beecham to form GlaxoSmithKline.

Cancer: United Therapeutics has tested treprostinil in preclinical studies as a potential anticancer agent and found that it has an antimetastatic. . . that given to patients with pulmonary hypertension. The company is currently conducting a phase I trial in patients with metastatic **cancer** worldwide. Treprostinil appears to exert its antimetastatic effect by blocking the PRAR endothelial cell receptor.

Licensees:Treprostinil is manufactured by SynQuest (United Therapeutics) in the USA. **Remodulin** sup(TM) for injection is manufactured by Baxter Pharmaceutical Solutions LLC in the USA.

United Therapeutics licensed patents for treprostinil from. . . in Australia.

Paladin Labs has exclusive distribution rights for treprostinil in Canada. However, in October 2002, following approval of **Remodulin** sup(TM) from the Canadian TPD, Paladin Labs is in discussion with United Therapeutics regarding distribution responsibilities; United Therapeutics is also pursuing pricing approval for **Remodulin** sup(TM).

AOP Orphan Pharmaceuticals has distribution rights for the product in Austria, Switzerland, and several Eastern European countries. Ferrer International. . . reported revenues of $US11.6 million in the second

quarter of 2002. The majority of the revenues were from sales of **Remodulin** sup(TM) and related infusion pumps and supplies - the product was launched in May 2002. In August 2002, approximately 500 patients were on **Remodulin** sup(TM) therapy worldwide, of which about 60% were considered to be 'reimbursable' patients - at the time, this was equating. . . all four of the Medicare Durable Medical Equipment Regional Carriers in the US have issued policies for nation-wide reimbursement of **Remodulin** sup(TM). Medicare is also to reimburse costs for infusion pumps and other related equipment needed by patients. The coverage is retroactive from May 21, 2002 - at this time, the recommended average wholesale price for **Remodulin** sup(TM) was $US65/mg, according to United Therapeutics.

L2 ANSWER 2 OF 20 ADISNEWS COPYRIGHT 2003 (ADIS)
TI Product news: US market news.
AN 2002:2612 ADISNEWS ED 31 May 2002 UP 31 May 2002
DN 11738324-800840998
TI Product news: US market news.

TI OTHER NEWS TO NOTE.
AN 2001:148291 NLDB
TI OTHER NEWS TO NOTE.
SO BIOWORLD Today, (29 Jun 2001) Vol. 12, No. 126.
PB American Health Consultants, Inc.
DT Newsletter
LA English
WC 1813
TX Cephalon Inc., of West Chester, Pa., said Actiq, for the management of breakthrough **cancer** pain in patients with malignancies who are receiving and who are tolerant to opioid therapy, was granted marketing authorization in. . .

Matrix Pharmaceutical Inc., of Fremont, Calif., began enrollment in a Phase II study in patients with primary liver **cancer** using IntraDose (cisplatin/epinephrine injectable gel). The open-label, multicenter study will evaluate 60 patients with hepatocellular carcinoma. Endpoints include tumor response,. . . filed a new drug application with the FDA in January for IntraDose to treat refractory or recurrent head and neck **cancer**.

MGI . . . Minneapolis, said the FDA granted fast-track designation for the use of irofulven, MGI's anticancer compound, in patients with gemcitabine-refractory pancreatic **cancer**. Irofulven is in a series of trials for the treatment of solid tumors and in a pivotal Phase III trial for patients with pancreatic **cancer**.

Telik Inc., of South San Francisco, started a Phase II trial with TLK286, its product for advanced non-small-cell lung **cancer**. Patients will receive TLK286 once every three weeks until disease progression. Telik initiated Phase II trials in colorectal **cancer** and ovarian **cancer** in March and May, respectively.

United . . . Silver Spring, Md., said the FDA's Cardiovascular and Renal Drugs Advisory Committee will discuss the benefit-to-risk profile of its drug, **Remodulin** (formerly UT-15), at its meeting scheduled Aug. 9-10.

L2 ANSWER 18 OF 20 PHARMAML COPYRIGHT 2003 MARKETLETTER
TI Actelion showing strong potential as Tracleer continues to drive growth
AN 1664501 PHARMAML
TI Actelion showing strong potential as Tracleer continues to drive growth
SO Marketletter July 29, 2002
DT Newsletter
WC 782
TX . . . a high price for Tracleer. Currently, only two other drugs are approved for PAH, GlaxoSmithKline's Flolan (epoprostenol) and United Therapeutic's **Remodulin** (treprostinil sodium), the latter having only just been launched (Marketletter June 3).
. . . orally-active urotensin II receptor antagonist which the firm expects to initiate by early 2003. Potential uses include metabolic, cardiovascular and **cancer** indications.

L2 ANSWER 19 OF 20 PHIC COPYRIGHT 2003 PJB

TI Major New US product approvals
AN 2003:3224 PHIC
DN S00789878
DED 19 Feb 2003
TI Major New US product approvals
SO Scrip (2003)
DT Newsletter
FS FULL

TX

Product	Company	Indication	Month	Type of review
Abilify (aripiprazole)	Otsuka/BMS	Schizophrenia	Nov	Standard
Alinia (nitazoxanide)	Romark	Infections	Nov	Priority/ orphan
Benicar (olmesartan medoxomil)	Sankyo	Hypertension	Apr	Standard
Eloxatin (oxaliplatin)	Sanofi-Synthelabo	Colorectal cancer	Aug	Priority
Extraneal (icodextrin)	Baxter Healthcare	Continuous ambulatory peritoneal dialysis	Dec	Standard/ orphan
Faslodex (fulvestrant)	AstraZeneca	Breast cancer	Apr	Standard
Hepsera (adefovir dipivoxil)	Gilead Sciences	Hepatitis B	Sep	Priority
Inspra (eplerenone)	Pharmacia	Hypertension	Sep	Standard
Orfadin (nitisinone)	Swedish Orphan	Hereditary tyrosinaemia type 1	Jan	Priority/ orphan
Relpax (eletriptan hydrobromide)	Pfizer	Migraine	Dec	Standard

TI AltaRex and United Therapeutics sign license agreement.(for the development of five monoclonal antibodies that activate the immune system to treat **cancer**)(Brief Article)
AN 2002:111722 NLDB
TI AltaRex and United Therapeutics sign license agreement.(for the development of five monoclonal antibodies that activate the immune system to treat **cancer**)(Brief Article)
SO BIOTECH Patent News, (1 Apr 2002) Vol. 16, No. 4.
ISSN: ISSN: 0898-2813.
PB Biotech Patent News
DT Newsletter
LA English
WC 765
TI AltaRex and United Therapeutics sign license agreement.(for the development of five monoclonal antibodies that activate the immune system to treat **cancer**)(Brief Article)
TX AltaRex . . . entered into an exclusive license agreement for the development of five monoclonal antibodies that activate the immune system to treat **cancer**. The strategic collaboration is centered on AltaRex's OvaRex (oregovomab) antibody that is currently in late-stage clinical development for the treatment of metastatic ovarian **cancer**. The four additional products are intended to treat lung, breast, prostate, multiple myeloma and other forms of **cancer**.

Under . . . a right of first refusal to any products developed or acquired by AltaRex which have applications in the treatment of **cancer**.

"I . . . United Therapeutics. "The AltaRex program may fit well with our ongoing assessment of the anti-metastatic properties of our lead drug, **Remodulin**, which is the subject of growing interest among **cancer** researchers."

"AltaRex . . . had been considering, the collaboration with United Therapeutics represents the best fit and the best value for our shareholders and **cancer** sufferers, all of whom we expect will share in the success of the company's oncology products and technology platform. We will continue to build our technology platform, both with United for the **cancer** field and on our own. Our collaboration with United Therapeutics affords us the opportunity to explore the application of our. . .

AltaRex . . . agents, specifically foreign monoclonal antibodies, to alter patients' immune system responses in a therapeutically beneficial manner for conditions that include **cancer**, infectious diseases and autoimmune diseases.

Subscription: $95.00 per year. Published monthly.. . .

L2 ANSWER 13 OF 20

TI Product setbacks cast gloom over industry. (Feature).(Biotech industry suffers late-stage product setbacks)
AN 2002:56072 NLDB
TI Product setbacks cast gloom over industry. (Feature).(Biotech industry suffers late-stage product setbacks)
SO BioVenture View, (19 Feb 2002) Vol. 17, No. 4, pp. 8(2).
ISSN: 0892-1903.
PB Pharmabooks Ltd.
DT Newsletter
LA English
WC 1147

TX While . . . stories are just around the corner. United Therapeutics recently received an approvable letter from the FDA for its prostacyclin analogue, **Remodulin**, for the treatment of pulmonary arterial hypertension. In the meantime, companies should analyse trials with the utmost care to make. . .

Dendreon	Provenge	Prostate **cancer**
lmClone Systems	Erbitux	Colorectal **cancer**
Sugen	SU5416	Colorectal **cancer**
Sugen	Ph III trial fails to meet endpoint SU5416 programme in colorectal **cancer** closed	

Subscription: $550.00 per year. Published monthly.